Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 131–137.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1206

JLCR

Research Article

Synthesis of ^{3}H, ^{14}C and $^{2}H_4$ labelled SCH 211803

D. HESK*, K. VORONIN, P. MCNAMARA, P. ROYSTER, D. KOHARSKI, S. HENDERSHOT, S. SALUJA, V. TRUONG and T. M. CHAN

Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth NJ 07033, USA

Received 21 November 2006; Revised 27 November 2006; Accepted 27 November 2006

Abstract: [^{3}H]SCH 211803, at a specific activity of 1.56 Ci/mmol, was prepared by direct exchange with tritiated water and platinum metal. [$^{2}H_4$]SCH 211803 was prepared from [^{2}H]formaldehyde in a seven step synthesis in 10% yield. [^{14}C]SCH 211803 was prepared from *N*-benzyl-4-hydroxy[2-^{14}C]piperidine in a four-step synthesis in 35% radiochemical yield. Additionally a high specific activity batch of [^{3}H]SCH 211803 was prepared by $Ru(Ph_3P)_3Cl_2$ catalysed exchange with 90 at% tritiated water to a specific activity of 35 Ci/mmol. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: SCH 211803; tritium; deuterium; carbon-14; synthesis

Introduction

SCH 211803 **1** (Figure 1), is a muscarinic-2 receptor antagonist[1–4] potentially useful as therapy for Alzheimer's disease. Four distinct isotopically labelled forms of SCH 211803 were synthesized. Low specific activity [^{3}H]SCH 211803 was prepared for a preliminary ADME evaluation of the compound and [^{14}C]SCH 211803 for more definitive ADME work. In addition high specific activity [^{3}H]SCH 211803 was prepared for protein binding work and [$^{2}H_4$]SCH 211803 was prepared as an internal standard for a LC-MS bioanalytical method.

This paper hence discusses the synthesis of low and high specific activity [^{3}H]SCH 211803, [$^{2}H_4$]SCH 211803 and [^{14}C]SCH 211803.

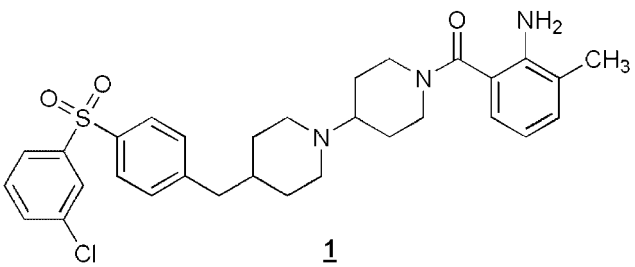
Results and discussion

Low specific activity [^{3}H]SCH 211803 was prepared by simple Pt catalysed exchange of the target molecule with the intention of labelling the aromatic rings in the sterically accessible meta positions as shown in Figure 2.

60 mCi of crude product @ 63% RCP was isolated from a reaction with 500 mCi of 50 Ci/ml tritiated water. After clean-up on a Silica 'Sep-Pak' and reverse phase hplc purification, 27.7 mCi at a specific activity of 1.56 Ci/mmol was isolated. ^{3}H nmr analysis showed the following distribution of tritium as shown in Figure 3.

Only 9.4% of the tritium was located in the expected aromatic positions. The majority (77.6%) was located in the piperidine rings. Although no systematic studies of Pt catalyzed exchange reactions of aliphatic amines have been published, it is possible that the basic piperidine nitrogen is involved in adsorption of the molecule onto the platinum surface. Such an effect has been observed in heterocyclic systems, such as that observed by Garnett and Long in the labelling of 3-picoline, where it was noted that most exchange took place adjacent to the nitrogen atom due to preferential absorption of the Pt catalyst on the nitrogen.[5]

High specific activity [^{3}H]SCH 211803 was prepared for plasma protein binding studies as shown in Figure 4.



1

Figure 1 SCH 211803.

*Correspondence to: D. Hesk, Schering Plough Research Institute, 2015 Galloping Hill Road, Kenilworth NJ 07033, USA.
E-mail: david.hesk@spcorp.com

Copyright © 2007 John Wiley & Sons, Ltd.

WILEY InterScience® DISCOVER SOMETHING GREAT

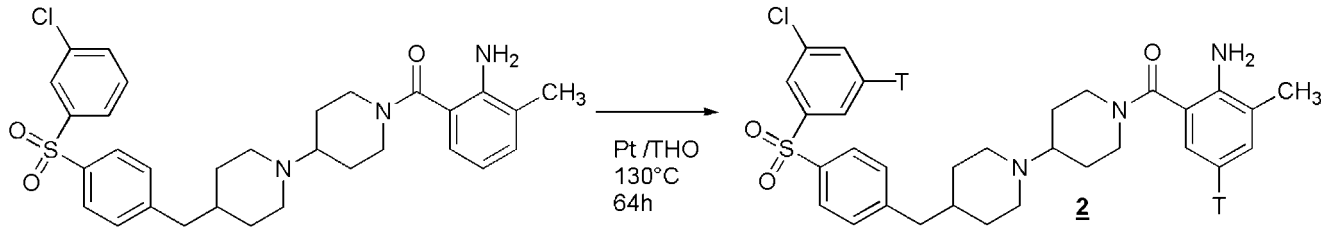


Figure 2 Synthesis of low specific activity [^{3}H]-SCH 211803.

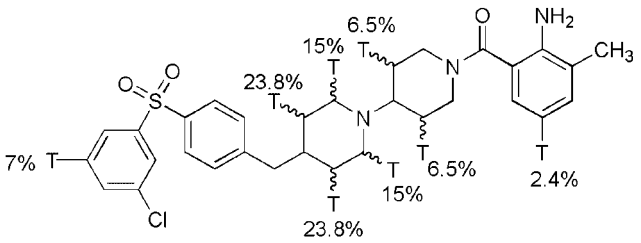


Figure 3 Low specific activity [^{3}H]-SCH 211803.

Labelling of piperidine **3** was carried out at Amersham with 20 Ci of 90 at% tritiated water and $Ru(Ph_3P)_3Cl_2$ as catalyst.[6] A total of 1.1 Ci of crude **4** was obtained. 200 mCi of crude **4** was purified on a silica 'Sep-Pak' to give 52 mCi of pure **4**. Finally, piperidine **4** was coupled with 3-methylanthranilic acid using EDCI/HOBT. After hplc purification, 46 mCi of **5**, at 31.1 Ci/mmol, was isolated. ^{3}H nmr showed tritium was located in the expected sites.

The synthesis of [$^2H_4$]SCH 211803 is shown in Figure 5.

The deuterium was incorporated via a Mannich type cyclization by reaction of a 20% solution of [$^2H_4$]formaldehyde in D_2O with benzylamine trifluoroacetate and trimethylallyl silane.[7] Compound **6** was obtained in 72% yield after silica gel chromatography. The benzyl group was removed in quantitative yield by hydrogenolysis and a Boc group added in modest yield by treatment with Boc anhydride. Perruthenate catalysed oxidation[8] of alcohol **8** gave [$^2H_4$]N-Boc-4-piperidinone **9** in 95% yield. Compound **11** was prepared in a two step, one pot procedure via condensation of ketone **9** and amine **10** to give an imminium ion that was reduced with $NaB(OAc)_3H$ to give amine **11**.[9] The crude product **11** was treated with acid to remove the Boc group in near quantitative yield to give **12**. Amine **12** was coupled with 3-methylanthranilic acid to give [$^2H_4$]SCH 211803. The crude product was purified by silica gel chromatography, 726 mg (60%) of [$^2H_4$]SCH 211803 **13** was obtained.

[^{14}C]SCH 211803 was synthesized from [^{14}C]formaldehyde using a route similar to the [$^2H_4$]SCH 211803 synthesis. *N*-benzyl-4-hydroxy[2-^{14}C]piperidine was prepared from [^{14}C]formaldehyde by Amersham Bioscience. Synthesis of [^{14}C]SCH 211803 is shown in Figure 6.

The synthesis followed closely the route to [$^2H_4$]SCH 211803 discussed previously with only minor changes in experimental details. After purification by silica gel chromatography and reverse phase hplc purification, 35 mCi (35% from *N*-benzyl-4-hydroxy[2-^{14}C]piperidine) of [^{14}C]SCH 211803 was obtained.

Experimental

Materials

Tritiated water (50 Ci/ml) and *N*-benzyl]-4-hydroxy[2-^{14}C]piperidine were purchased from Amersham Biosciences. [$^2H_2$]formaldehyde was purchased from Cambridge Isotope Laboratories. Compounds **3** and **10** were obtained from Schering-Plough Research Institute, Chemical Development. Tris-triphenyl phosphine ruthenium (II) chloride was purchased from Alfa. All remaining reagents and solvents were purchased from Aldrich or Acros Organics and were used as received. All ^{14}C and ^{2}H steps were carried out under an atmosphere of argon.

Liquid scintillation counting

Quantitation of radioactivity was performed using a Packard 2200CA liquid scintillation analyser, with Scintiverse BD cocktail used throughout.

Thin layer chromatography

Thin layer chromatography was performed using Whatman LK6DF (silica gel 60) 5×20 cm, 0.25 mm plates. The plates were scanned on a Bioscan 1000 linear analyzer. The following systems were used:

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr

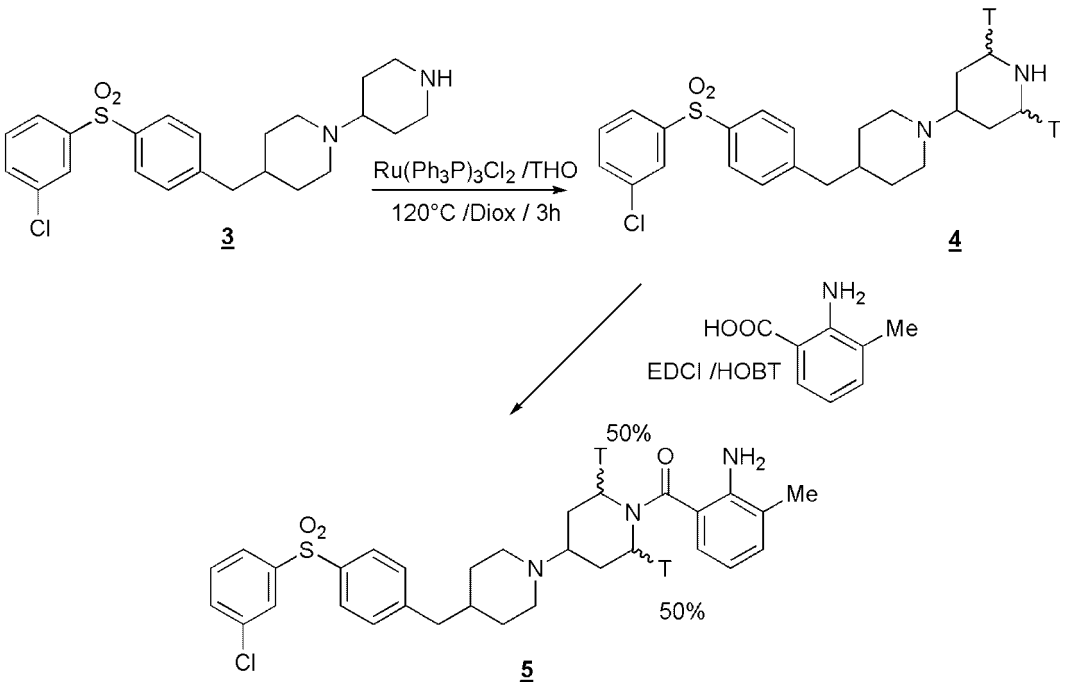


Figure 4 Synthesis of high specific activity [^{3}H]-SCH 211803.

(1) Methylene chloride:methanol:ammonium hydroxide (90:10:1)
(2) Methylene chloride:2 M methanolic ammonia (80:20)
(3) Methylene chloride:methanol (90:10)

High performance liquid chromatography

A Waters 600E system controller was used with a Waters 717 auto injector. Chemical purity was determined using a Waters 2487 dual channel UV detector and radiochemical purity using a Radiomatic 525TR radioflow detector with Radiomatic Flo-Scint III liquid scintillation cocktail. The following systems were used:

(1) Zorbax SB-C18 150 mm × 4.6 mm ID, 0.05 M pH 3.5 triethylammonium acetate: acetonitrile (65:35) for 20 min followed by a step gradient to acetonitrile, 1 ml/min, 254 nm.
(2) Zorbax Extend C18 150 mm × 4.6 mm ID, 0.05M pH 9 ammonium carbonate: acetonitrile (45:55) for 15 min followed by a step gradient to acetonitrile, 1 ml/min, 244 nm.
(3) YMC basic, 100 mm × 4.6 mm ID, 0.1% Aq trifluoroacetic acid: methanol: *n*-propanol (55.5: 41.5: 3) for 15 min followed by a step gradient to (10: 87: 3), 1 ml/min, 244 nm.
(4) Phenomenex Luna C18(2) 150 mm × 4.6 mm ID, pH 8 0.05 M ammonium carbonate: acetonitrile (45:55) for 15 min followed by a step gradient to acetonitrile, 1 ml/min, 244 nm.

Synthesis of (^{3}H)-SCH 211803 (2)

(^{3}H)-1,4′-Bipiperidine-, 1′- ((2–amino-3-methylphenyl) carbonyl)-4-((4-((3-chlorophenyl) sulphonyl) phenyl methyl) (2). Platinum dioxide (15 mg) was suspended in water (10 ml) and sodium borohydride (80 mg) was added over 10 min. After the effervescence had ceased, the flask was warmed to 70°C for 30 min. The water was decanted off and the platinum metal washed with water (3 × 10 ml) and acetone (3 × 10 ml). Finally the platinum metal was transferred to a thick walled glass ampoule (0.313″ OD × 0.078″ wall) containing SCH 211803 **1** (25 mg) and dioxane (100 μl). The ampoule was fitted with a rubber septum and tritiated water (50 Ci/ml, 500 mCi) was added via a syringe. The ampoule was frozen in liquid nitrogen, evacuated and sealed in a flame, before being placed in an oil bath at 130°C for 64 h. After the reaction was complete, the contents of the ampoule were partitioned between potassium hydroxide solution (1 M, 5 ml) and methylene chloride (5 ml). The methylene chloride layer was removed and the aqueous layer extracted with methylene chloride (2 × 5 ml). The combined methylene chloride extracts were washed with water and evaporated to dryness to yield 60 mCi of crude product **2**,

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr

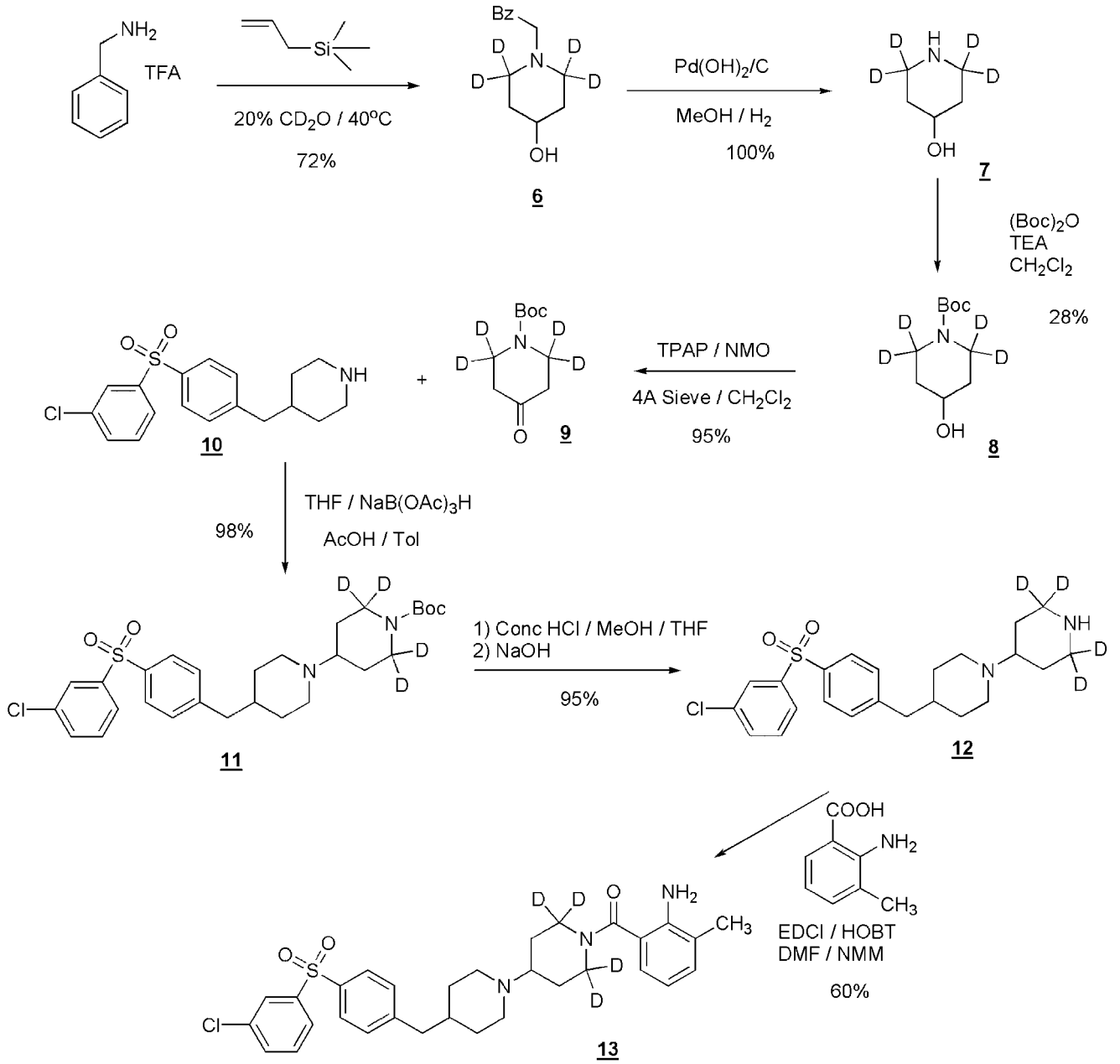


Figure 5 Synthesis of [$^2H_4$]-SCH 211803.

with a radiochemical purity of 63% (tlc system 1). Initial purification was carried out on a 1 g Waters Silica 'Sep-Pak' cartridge using a gradient of 1–2% 2M methanolic ammonia in methylene chloride. Final purification was carried out by hplc on a 250 mm × 9.4 mm ID Zorbax SB C18 column with a mobile phase of 0.05 M pH 3.5 aqueous triethylammonium acetate: acetonitrile (68:32) at a flow rate of 5 ml/min. Detection was at 254nm. A total of 27.5 mCi at a specific activity of 1.56 Ci/mmol was isolated. The radiochemical purity was greater than 99% (hplc system 1 and tlc system 1). ^3H NMR: $CDCl_3$ 25°C, δ7.44, δ6.63, δ2.84, δ2.05, δ1.77, δ1.55, δ1.41, δ1.21 ppm.

Synthesis of (^3H)-SCH 211803 (5)

1,4′-Bipiperidine-(2′6′-^3H), 4-((4-((3-chlorophenyl)sulphonyl)phenyl)methyl) (4). Compound **3** (30 mg) and tristriphenylphosphine ruthenium chloride (3 mg) were

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr

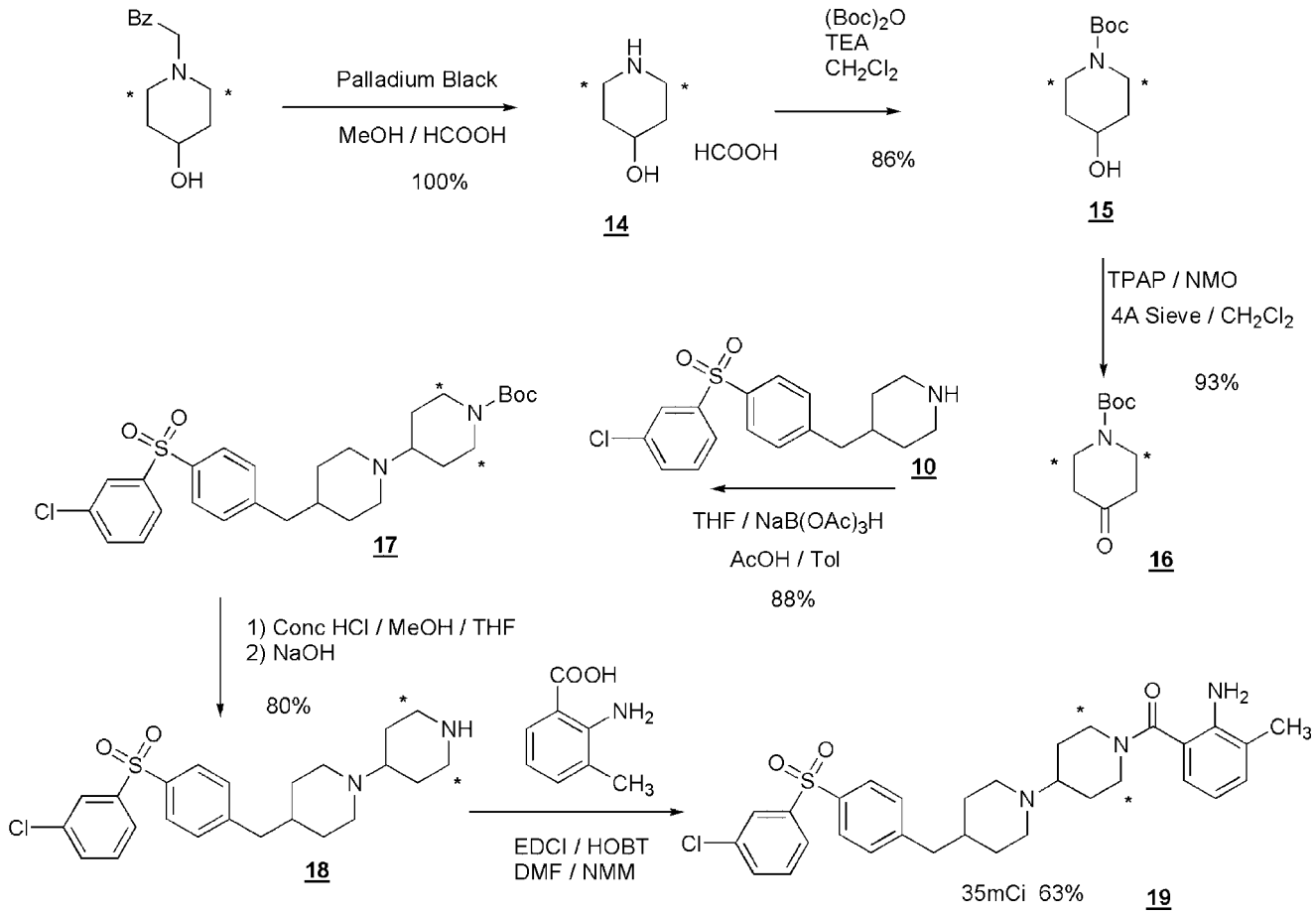


Figure 6 Synthesis of [^{14}C]-SCH 211803.

suspended in dioxane (100 µl) in a tritiation vessel. Tritiated water (90 at%, 20 Ci) was distilled in, and the tube was sealed and heated in a furnace for 3 h at 120°C. After the reaction was complete, the contents of the tube were dissolved in ethanol (5 ml) and evaporated to dryness. The residue was dissolved in ethanol (5 ml) and the labile removing process was repeated twice more. A total of 1.1 Ci of crude product **4** at a radiochemical purity of 50% (tlc system 1) was isolated. 200 mCi of **4** was purified on a Waters 1 g silica 'Sep-Pak' cartridge using a gradient of 5–10% 2 M methanolic ammonia in methylene chloride as eluent. A total of 52.4 mCi **4** at a radiochemical purity of 80% was isolated (tlc system 2), which was used directly in the next step.

1,4′-Bipiperidine-(2′6′-^{3}H),1′-((2-amino-3-methylphenyl)carbonyl)-4-((4-((3-chlorophenyl)sulphonyl)phenyl)methyl) (^{3}H)SCH 211803 (5). Compound **4** was dissolved in DMF (0.4 ml) and 3-methylanthranilic acid (5.6 mg, 0.037 mmol), 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide hydrochloride (7.2 mg, 0.038 mmol) and 1-hydroxybenzotriazole hydrate (5.1 mg, 0.037 mmol) were added. The reaction was stirred at room temperature for 48 h (tlc system 1), before it was partitioned between methylene chloride (2 ml) and aqueous sodium hydroxide solution (1 M, 1 ml). The organic layer was removed and the aqueous layer extracted with methylene chloride (2 × 2 ml). The combined organic layers were dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The product was purified on a 250 mm × 9.4 mm Zorbax Extend C18 column with a mobile phase of 0.05 M pH9 triethylammonium acetate: acetonitrile (1:1) at flow rate of 5 ml/min. Detection was at 254 nm. A total of 46.2 mCi of [^{3}H]SCH 211803 **5** at a specific activity of 31.1 Ci/mmol was isolated. The radiochemical purity was greater than 99% (hplc systems 2 and 3). ^{3}H NMR, $CDCl_3$ −20°C, δ4.78, δ3.90, δ2.97, δ2.69 ppm.

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr

Synthesis of ($^2H_4$)-SCH 211803 (13)

***N*-Benzyl-2,6($^2H_4$)-4-hydroxypiperidine (6)**. A 20% solution of [$^2H_2$]-formaldehyde in D_2O (36.1 ml, 260 mmol) was added to benzylamine trifluoroacetate (25 g, 113 mmole) and the resulting mixture sonicated for 10 min and then stirred for 1 h at room temperature. To the resulting clear solution was added allyltrimethylsilane (19.8 ml, 124 mmol) and the reaction was heated at 40°C overnight. The resulting two phase mixture was diluted with water (50 ml) and solid potassium carbonate was added until the pH was greater than pH 9. The product was extracted with ether (3 × 45 ml), the layers were combined, dried over anhydrous sodium sulphate, filtered and evaporated to an oil. The product was purified by silica gel chromatography using a gradient of 10–50% methanol in methylene chloride as eluent to yield 16 g (72%) of Compound **6**.

2,6-($^2H_4$)-4-Hydroxypiperidine (7). Compound **6** (2.03 g, 10.4 mmol) and Pearlman's catalyst (0.5 g) were dissolved in methanol (20 ml) and hydrogenated on a Parr shaker at 35 psi overnight. After tlc (tlc system 3) showed complete reaction, the reaction mixture was filtered through celite and evaporated to dryness to yield 1.09 g (100%) of **7**, which was used directly in the next step.

***N*-Boc-2,6-($^2H_4$)-4-hydroxypiperidine (8)**. Compound **7** (1.0 g, 9.5 mmol) was dissolved in anhydrous methylene chloride (10 ml) and triethylamine (3 ml). Di-tert-Boc-dicarbonate (2.5 g, 11.4 mmol) was added and the reaction mixture was stirred at room temperature overnight (tlc system 3). The reaction mixture was diluted with ether (60 ml) and washed with sodium bisulphate solution (1 M, 2 × 20 ml) and sodium bicarbonate solution (0.3 M, 10 ml). The ether layer was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give the crude product as a clear oil. The batch was purified by silica gel chromatography using a gradient of 1–2% methanol in methylene chloride to yield 547 mg (28%) of **8**.

***N*-Boc-2,6-($^2H_4$)-4-piperidinone (9)**. Compound **8** (547 mg, 2.66 mmole) was dissolved in methylene chloride (20 ml) and cooled to 0°C. 4Å molecular sieves (821 mg) and *N*-methylmorpholine-*N*-oxide (468 mg, 3.99 mmole) were added followed by tetrapropylammonium perruthenate (48 mg, 0.14 mmole). The reaction was stirred at 0°C for 15 min and then at room temperature for 90 min, after which tlc (tlc system 3) showed complete conversion. The reaction solution was evaporated to dryness and purified by silica gel chromatography using a gradient of 1–2% methanol in methylene chloride as eluent. A total of 515 mg (95%) of **9** was isolated after vacuum drying overnight.

(1,4′-Bipiperidine- (2′,6′-$^2H_4$)) -1′ -carboxylic acid, 4-((4-((3-chlorophenyl) sulphonyl) phenyl) methyl)-, 1,1′-dimethylethyl ester (11). To a solution of Compound **10** (688 mg, 2.3 mmole) in toluene (40 ml) was added Compound **9** (515'mg, 2.53 mmole). The mixture was heated to reflux temperature for 15 min, and then the toluene was removed by distillation. Additional portions of toluene (3 × 50 ml) were added and the distillation continued until a final volume of 2–3 ml was reached. After allowing to cool to room temperature, tetrahydrofuran (4 ml) was added followed by sodium triacetoxyborohydride (585 mg, 2.76 mmol) and the reaction stirred for 1 h. Acetic acid (0.1 ml) was added and the stirring continued for a further 30 min after which tlc (tlc system 3) showed complete reaction. Acetic anhydride (0.04 ml) was added, followed by water (6 ml), THF (6 ml) and the two phase mixture was stirred for 10 min. The THF layer was removed and the aqueous layer extracted with THF (2 × 10 ml). The combined THF layers were dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield 1.2 g (98%) of 11, which was used directly in the next step.

1,4′-Bipiperidine-(2′6′-$^2H_4$), 4-((4-((3-chlorophenyl)sulphonyl)phenyl)methyl) (12). Compound **11** (1.2 g, 2.24 mmol) was dissolved in a mixture of THF (2 ml) and methanol (8 ml) and cooled to 0°C. Concentrated HCl (2 ml) was then added dropwise and the reaction stirred at room temperature for 6 h at which point tlc (tlc system 3) showed complete conversion. The reaction was re-cooled in an ice bath and concentrated ammonium hydroxide solution was added dropwise until a pH of 11 was achieved. The product was then extracted with methylene chloride (2 × 20 ml). The organic extracts were pooled, dried over anhydrous sodium sulphate, filtered and evaporated to dryness to yield 931 mg (95%) of **12**, which was used directly in the next step.

1,4′-Bipiperidine- (2′6′-$^2H_4$), 1′- ((2-amino-3 methylphenyl) carbonyl)-4-((4-((3-chlorophenyl)sulphonyl)phenyl)methyl) ($^2H_4$)SCH 211803 (13). Compound **12** (931 mg, 2.13 mmol) was dissolved in anhydrous DMF (10 ml) and cooled to 0°C. To this solution were added 3-methylanthranilic acid (373 mg, 2.47 mmol), 1-(3-dimethyl amino propyl)-3-ethyl carbodiimide hydrochloride (653 mg, 3.41 mmol), 1-hydroxybenzotriazole hydrate (345 mg 2.55 mmole) and *N*-methylmorpholine (0.59 ml, 5.33 mmol). The reaction was stirred at room

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr

temperature overnight (tlc system 3) and then diluted with water (7 ml), concentrated ammonium hydroxide (1 ml) and ethyl acetate (7 ml). The ethyl acetate layer was removed and the remaining aqueous fraction extracted with ethyl acetate (10 ml). The combined ethyl acetate layers were washed with water (2×10 ml), dried over anhydrous sodium sulphate, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography using a gradient of 1–4% 2 M methanolic ammonia in methylene chloride as eluent. A total batch of 696 mg (60%) was isolated. Analysis by hplc (hplc system 1) gave a chemical purity of 98.8%. FAB^+ Mass spectrometry unlabelled SCH 211803 **1**: *m/z* 566 (M), [$^{2}H_4$]SCH 211803 **13**: *m/z* 570 (M). ^{1}H nmr analysis in $CDCl_3$ at $-16^{\circ}C$ confirmed resonances at δ4.78, δ3.91, δ3.00, δ2.71 ppm observed in unlabelled SCH 211803 **1** were absent in the spectrum of [$^{2}H_4$]SCH 211803 13.

Synthesis of (^{14}C)SCH 211803 (19)

2,6-(^{14}C)-4-Hydroxypiperidine (14). *N*-Benzyl-4-hydroxy-[2,6-^{14}C]-piperidine (100 mCi, 171 mg, 0.88 mmol) and palladium black were mixed with a 8% solution of formic acid in methanol (10 ml) and the resulting suspension stirred overnight. After tlc (tlc system 3) showed complete reaction, the reaction mixture was filtered through a pad of Celite, which was washed with methanol (25 ml) and 8% formic acid in methanol (10 ml). The filtrate was evaporated to dryness to yield **14** (100 mCi) and used directly in the next step.

***N*-Boc-4-hydroxy-(2,6-^{14}C)-piperidine (15)**. Compound **15** was prepared from 100 mCi, 0.88 mmol of **14** via the procedure previously described for Compound **8**, to yield a total of 86 mCi (86%).

***N*-Boc-(2,6-^{14}C)-4-piperidinone (16)**. Compound **16** was prepared from 86 mCi, 0.755 mmol of **15** via the procedure previously described for Compound **9**, to yield a total of 80 mCi (93%).

(1,4′-Bipiperidine- (2′,6′-^{14}C)) -1′ -carboxylic acid, 4-((4-((3-chlorophenyl) sulphonyl) phenyl) methyl)-, 1,1′-dimethylethyl ester (17). Compound **17** was prepared from 80 mCi, 0.70 mol of **16** and 0.67 mmol of **10** via the procedure described previously for Compound **11**, to yield a total of 70 mCi (80%).

1,4′-Bipiperidine-(2′6′-^{14}C), 4-((4-((3-chlorophenyl)sulphonyl)phenyl)methyl) (18). Compound **18** was prepared from 70 mCi, 0.61 mmol of 17 via the procedure described previously for Compound **12**, to yield a total of 56 mCi (80%).

1,4′-Bipiperidine- (2′6′-^{14}C), 1′- ((2 -amino -3- methylphenyl) carbonyl)-4- ((4-((3-chlorophenyl)sulphonyl)-phenyl)methyl) (^{14}C)SCH 211803 (19). Compound **19** was synthesized from 56 mCi, 0.49 mmol of **18** via the procedure described previously for Compound **13**. After initial purification on silica gel, the product was further purified by preparative hplc on a 9.4×250 mm Zorbax XDB C18 column with a mobile phase of acetonitrile (1:1) 0.05 M pH 7.5 triethylammonium acetate at a flow rate of 5 ml/min. Detection was at 254 nm. A total batch of 35 mCi (63%) of [^{14}C]SCH 211803 **19** at a specific activity of 193 μCi/mg, 110 mCi/mmol was isolated. The radiochemical purity as determined by hplc systems 3 and 4 was greater than 98%. FAB^+ Mass spectrometry unlabelled SCH 211803 **1**: *m/z* 566 (M), [^{14}C]SCH 211803 **19**: *m/z* 570.

REFERENCES

1. Wang Y, Chackalamannil S, Hu Z, Clader JW, Greenlee WJ, Billard W, Binch H III, Crosby G, Ruperto V, Duffy RA, McQuade R, Lachowicz JE. *Biorg Med Chem Lett* 2000; **10**: 2247.
2. Greenlee WJ, Clader JW, Asberom T, McCombie S, Ford J, Guzik H, Kozlowski J, Li S, Liu C, Lowe D, Vice S, Zhao H, Zhou G, Billard W, Binch H III, Crosby G, Duffy R, Lachowicz JE, Coffin VL, Watkins R, Ruperto V, Strader C, Taylor L, Cox K. *Farmaco* 2001; **56**: 247.
3. Billard W, Binch H, Bratzler K, Chen LY, Crosby G, Duffy RA, Dugar S, Lachowicz JE, McQuade R, Pushpavanam P, Ruperto V, Taylor L, Clader JW. *Biorg Med Chem Lett* 2000; **10**: 2209.
4. Wang Y, Chackalamannil S, Hu Z, Greenlee WJ, Clader JW, Boyle CD, Kaminski JJ, Billard W, Binch H III, Crosby G, Ruperto V, Duffy RA, Cohen-Williams M, Coffin VL, Cox KA, Grotz DE, Lachowicz JE. *J Med Chem* 2002; **45**: 5415.
5. Garnett JL, Long MA, Lukey CA, Williams PG. *J Chem Soc Perkin Trans* 1982; **2**: 287.
6. Hesk D, Koharski D, Saluja S, McNamara P, Magatti C, Cesarz D, Hendershot S, Jones JR. In *Synthesis and Applications of Isotopically Labelled Compounds*, Heys JR, Melillo DG (eds). Wiley: New York, 1997; 439.
7. Larsen SD, Grieco PA, Fobare WF. *J Am Chem Soc* 1986; **108**: 3512.
8. Brewer JC, Gray HB. *Anal Phys Inorg Chem* 1990; **2**: 121.
9. Abdel-Magid AF, Maryanoff CA, Carson KG. *Tetrahedron Lett* 1990; **31**: 5595.

Copyright © 2007 John Wiley & Sons, Ltd.

DOI: 10.1002.jlcr